UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/609,019	06/26/2003	Richard K. Cooper	51687-0101 (287015)	8431

23370 7590 05/04/2007

JOHN S. PRATT, ESQ
KILPATRICK STOCKTON, LLP
1100 PEACHTREE STREET
ATLANTA, GA 30309

EXAMINER	
SINGH, ANOOP KUMAR	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
05/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/609,019	COOPER ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21 and 52-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21 and 52-74.76-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/9/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment to the specification and claims filed April 9, 2007, has been received and entered. Applicants have amended claims 1, 52 and 63, while claims 22-51 have been canceled. Applicants election on telephone and reaffirmation of the telephonic election with traverse of the invention of group I (Claims 1-21) was acknowledged.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/09/2007 has been entered.

Withdrawn-Claim Objections

The objection to claim 1, 52 and 63 is withdrawn in view of amendments to the claims.

Withdrawn-Claim Rejections - 35 USC § 112

Claims 1-21, 52-80 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of amendments to the independent claims. It is noted that applicants have amended the claims to remove recitation of plurality of first ten codon and amended the claims to specifically recite that the transposase gene is modified such that plurality of the codons of the transposase gene that encodes for amino acid 2-10 of the transposase protein are individually modified.

Withdrawn -Claim Rejections - 35 USC § 112

Claims 1-21, 52-80 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in view of amendments to independent claims 1, 52, and 63. It is noted that as amended claims specifically recite that the transposase gene is modified such that plurality of the codons of the transposase gene that encodes for amino acid 2-10 of the transposase protein are individually modified and not plurality of first ten codon.

Withdrawn-Claim Rejections - 35 USC § 112

Claims 1-21, 52-80 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendments to claims 1, 52 and 63. Applicants have amended claims to clearly indicate that first codon of modified transposase gene is not modified.

New-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 8-10, 15-17 and 52-53, 61-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cooper R. (US 5,719,055, IDS), Williamson et al (Appl Environ Microbiol. 1994 March; 60(3): 771–776, IDS) and Savakis et al (US Patent application 20030150007, dated 8/7/2003, filing date 8/17/2002, effective filing date 4/7/2000, IDS).

Cooper taught a vector comprising a gene encoding a transposase operably linked to a promoter, Mo transposon insertion sequences recognized by the transposase; and an exogenous gene located between the transposon insertion sequences. The promoter directing expression of the transposase gene may be inducible. See the claims. In column 8, at lines 58-67 Cooper listed transposases, including Tn10 and Tn5, which may be used in combination with the same vector. The claims require a modified transposase gene, wherein two to ten codons, are modified by changing a nucleotide at a third base position of the codon to an adenine or thymine without changing the amino acid encoded by the codon. Cooper et al discussed use of both constitutive and inducible promoters for directing expression of both the transposase gene and the gene of interest. See for example, columns 15-18. Cooper sought to express transgenes in various vertebrates as evidenced by the teachings in column 9, in lines 40-50. Cooper differed from the claimed invention by not teaching a promoter comprising a modified Kozak sequence that comprises ACCATG or a vector comprising more than one gene of interest operably linked to more than one promoter between the transposase insertion sequences.

It is noted that other transposase vectors were known at the time of filing of this application. Savakis et al use of modified transposon wherein the modification includes removal or disruption of transposase sequences or the incorporation of one or more heterologous coding sequences and/or expression controls sequences (see para. 23 of the published application). Although, Savakis et al exemplified type-2 transposon such as Minos to generate transgenic animal, however, he generally embraced the idea of using any natural transposon (see para 22). It is noted that Savakis et al contemplate heterologous to genetic sequences that are from a species other than the organism or transposon of interest (see para. 24 of the published application). Savakis et al disclose variety of promoters that could be used including tissue-specific promoters, and inducible promoters (para 26). It is also noted that Savakis et al also contemplates that the sequence of the transposase may be modified to optimize codon usage and thus, increase transposition frequencies. It is noted that Savakis et al describe that optimization of codon usage by converting less frequently used codons to more

frequently used codons is a method well known in the art to increase the expression levels of a given gene (see para. 143). However, Savakis et al differed from claimed invention by not disclosing modified prokaryotic transposase comprising Kozak sequence.

However, at the time the claimed invention was made inclusion of a Kozak sequence in an expression vector for optimal translation initiation of a gene in vertebrate cells was within the routine skill level of the ordinary artisan. It was also well known at the time the invention was made that an expression cassette may comprise gene of interest in operable linkage with one or more than one promoter. Prior to instant invention, it was generally known in the art that initiation codon of a prokaryotic gene such as one disclosed by Williamson would not be functional in a eukaryotic system unless it is modified to include a Kozak sequence. It is noted that most of the prior art generally teaches that initiation of eukaryotic mRNA translation occur exclusively at AUG Codons (see page 773, col. 1, last para). Williamson teach modifying the 5' end of a prokaryotic gene to include a eukaryotic start codon, the Kozak expression start site consensus sequence to facilitate manipulation of the gene (see abstract and entire article). Williamson et al teach expression of the prokaryotic gene lysostaphin and processing of the precursor to produce active secreted enzyme in eukaryotic system. However, Williamson differed from claimed invention by not teaching prokaryotic transposase gene that is codon optimized.

Accordingly, in view of the teachings of Cooper, Williamson and Savakis, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the vector of Cooper by inserting a Kozak sequence in the promoter such that is in operable linkage with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as Williamson et al specifically indicated that any initiation codon of a prokaryotic gene would not be functional in a eukaryotic system unless it is modified to include a Kozak sequence. One of ordinary skill in the art would have been sufficiently motivated to position Kozak sequence so as to include at least first codon of a prokaryotic gene in order for efficient translation initiation in a eukaryotic system in view

of disclosure by Williamson. In addition, It is evident that the person of ordinary skill would have optimized the transposase gene, because Savakis et al had already described that transposase may be modified to optimize codon usage to direct expression of different gene of interest in different host with increased transposition frequencies. It is emphasized that changing codon by individually modifying wild type sequence of CG at third base position of the codon to A or T is routine optimization depending upon transgene and host species as per the teaching of Savakis.

One who would practiced the invention would have had reasonable expectation of success because Williamson et al had already described use of Kozak sequence to express transposase gene in eukaryotic system. Williamson et al specifically taught that a Kozak sequence comprising ACCATG is the optimal sequence for initiating translation in vertebrate cells and it would have only required routine experimentation to modify the vector to Cooper to include Kozak sequence upstream of transposase and 3' to the promoter and further optimize the codon as per the requirement of transgene and host cell as per the teaching of Savakis.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-11, 15-21, 52-53, 57-62, 73-74, 76, 78 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cooper R. (US 5,719,055), Williamson et al (Appl Environ Microbiol. 1994 March; 60(3): 771–776) and Savakis et al (US Patent application 20030150007, dated 8/7/2003, filing date 8/17/2002, effective filing date 4/7/2000), Hackett et al (US Patent no. 6489458, dated 12/3/2002, filing date 9/10/1998, IDS), MacArthur et al (US Patent no. 6825396 dated 11/30/2004, filing date 4/18/1997, IDS).

The combined teachings of Cooper, Williamson et al and Savakis have been discussed above and are relied upon in same manner here. However, none of the references explicitly teaches advantage of using ovalbumin or other egg directing sequences.

MacArthur et al teach vector comprising the control elements that include an enhanced promoter directing the expression of the transgene in the oviduct, an untranslated region 5' to the structural gene (coding region) of appropriate length and sequence to promote efficient translation, and a signal sequence directing the secretion of the transgene product in the egg white (col.3, lines 1-6).. MacArthur et al teach the promoter may be ovalbumin, lysozyme, conalbumin and ovomucoid promoters and combinations thereof (See col. 7, lines 30-40). MacArthur et al also contemplate that the control sequences include a promoter directing the expression of the transgene in the liver and a signal sequence directing the uptake and secretion of the transgene product into the egg yolk-using promoter such as vitellogenin or combinations thereof (see col. 7, lines 40-45). MacArthur et al disclose control elements, which flank the transgene, include promoters and enhancers that could be used (col. 4, lines 64-65) including tissue-specific promoters. MacArthur et al teach that the vector's 5' untranslated region (UTR) very closely resembles that of ovalbumin RNA with only difference is a one base mutation near the 5' end which was necessary for construction and a 77 base leader is more consistent with Kozak's that is required for maximum translational efficiency. It is noted that MacArthur et al contemplated any UTR with a functional sequence around the start codon could be used for enhancing translational efficiency (See col. 9, lines 1-9). MacArthur et al disclose use of standard stop codons and the polyadenylation signal are included 3' to the structural gene (See col. 9, line 53-55). It is also noted that MacArthur et al emphasize the usefulness of providing gene to an avian or chicken cell, wherein the gene is expressed in the hen's oviduct and secretion of the gene product is in the hen's eggs. However, MacArthur et al do not disclose using ovalbumin or any other promoter with transposon-based vector. Prior to instant invention, use of control elements that included promoters was generally routine in the art. Hackett et al disclose variety of promoters that could be used including constitutive promoters, tissue-specific promoters, and inducible promoters (column 12, lines 35-40) to express transgene. It is also noted that Hackett also contemplates a particular DNA sequence could be modified to employ the codons preferred for a particular cell type. In addition, Hackett et al also disclose different nucleic acid encoding protein including growth hormone and insulin

comprising a promoter such as ovalbumin promoter that could direct expression of transgene for the production of recombinant protein in milk, urine, blood or eggs (column 16, lines 20-45). Furthermore, Hackette et al also disclose tagging of an exogenous gene and teach isolating the tagged gene (see example 7 and 8)

However, MacArthur and Hackett et al differed from claimed invention by not disclosing control elements in vector comprising prokaryotic transposase gene.

Accordingly, in view of the teachings of Cooper, Williamson and Savakis, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the vector of Cooper by inserting a Kozak sequence in the promoter such that is in operable linkage with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as Williamson et al specifically indicated that any initiation codon of a prokaryotic gene would not be functional in a eukaryotic system unless it is modified to include a Kozak sequence. One of ordinary skill in the art would have been sufficiently motivated to position Kozak sequence so as to include at least first codon of a prokaryotic gene in order for efficient translation initiation in a eukaryotic system in view of disclosure by Williamson (supra). Furthermore, Savakis et al provided motivation to modify the wild type transposase gene to optimize codon usage to direct expression of different gene of interest in different host with increased transposition frequencies. It is emphasized that changing codon by individually modifying wild type sequence of C or G at third base position of the codon to A or T is routine optimization depending upon transgene and host species as per the teaching of Savakis. The person of ordinary skill would be further motivated to modify the vector by including control elements including a signal sequence and using promoter such as ovalbumin, lysozyme, conalbumin and ovomucoid s (supra) as per the teaching of MacArthur and Hackett to express gene in milk or egg.

One who would practiced the invention would have had reasonable expectation of success because MacArthur/ Hackett had already described that signal sequence and promoters that could be used to direct expression of the transgene in milk or egg. Williamson and Savakis had already described use of Kozak sequence to express

transposase gene in eukaryotic system and optimization of codon usage depending of cell and transgene. Thus, it would have only required routine experimentation to modify the vector to Cooper to include Kozak sequence upstream of transposase and 3' to the promoter such as ovalbumin to direct expression of the gene in egg or milk.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-21, 52-74, 76, 78 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cooper R. (US 5,719,055, IDS), Williamson et al (Appl Environ Microbiol. 1994 March; 60(3): 771–776, IDS) and Savakis et al (US Patent application 20030150007, dated 8/7/2003, filing date 8/17/2002, effective filing date 4/7/2000, IDS), Hackett et al (US Patent no. 6489458, dated 12/3/2002, filing date 9/10/1998, IDS) or MacArthur et al (US Patent no. 6825396 dated 11/30/2004, filing date 4/18/1997, IDS) and further in view of Wallace, R. A, King J.L and Sanders, G.P., (Biology: The Science of Life, 1986, Scott Foresman and Company, pp 235, IDS).

The combined teachings of Cooper, Williamson et al, Savakis and MacArthur /Hackett have been discussed above and are relied upon in same manner here. However, none of the references explicitly teaches using two-stop codon with Poly A.

Prior to filing of this application, Wallace et al teach three stop codons UAA, UAG and UGA that are used as stop codon. It is noted that Wallace et al also disclose double stop codon such as UAA-UAG to ensure message to ribosome (pp 235, col. 2, see section polypeptide chain termination).

Accordingly, it would have been obvious and within the scope of skill for an artisan to subject the vector taught by Cooper, Williamson, Savakis and MacArthur /Hackett to include two-stop codon operably linked to the transposase as taught by Wallace. MacArthur et al had already taught use of standard stop codons and the polyadenylation signal. One of ordinary skill in the art would have been motivated to include multiple-stop codon to ensure proper termination of transposase synthesis and would have also included poly A as a obvious modification for expression in mammalian system. It is emphasized that a conalbumin Poly A broadly encompasses Poly A or any

signal and does not require entire non-coding region of a conalbumin for instant rejection.

One who would practiced the invention would have had reasonable expectation of success because Wallace had already described use of two stop codon to ensure polypeptide chain termination. It would have only required routine experimentation to modify the vector to include two stop codons operably linked to the gene to enhance the termination of transposase synthesis.

Therefore, the claimed invention would have been prima facie obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

No claims allowed.

The following art made of record and not relied upon is considered pertinent to applicant's disclosure: Herrero et al (Journal of Bacteriology, 1990, 6557-6567, IDS).

Zhang e al (WO 01/83786, dated 11/8/2001)

Claims 75 and 80 are free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anoop Singh, Ph.D.
AU 1632

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER